



Armed Forces College of Medicine AFCM



Neurotropic vitamins (B1 & B12)

By

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INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

- 1. Distinguish the active forms and functions of vitamins (B1 & 12)**
- 2. Correlate vitamins (B1& B12) deficiencies to their clinical disorders**

Case scenario



22 years old woman was brought to the emergency unit complaining of **respiratory distress**, **vomiting**, and **weakness**. Examination revealed

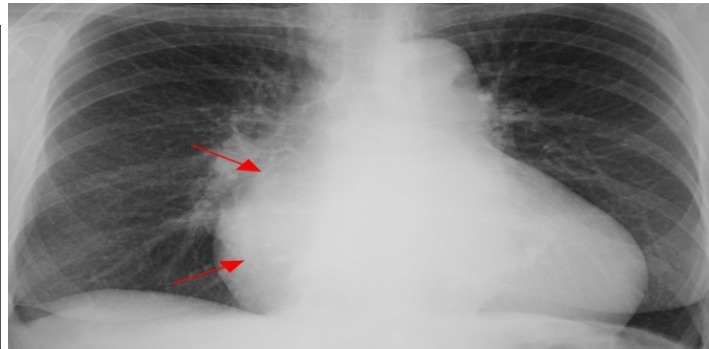
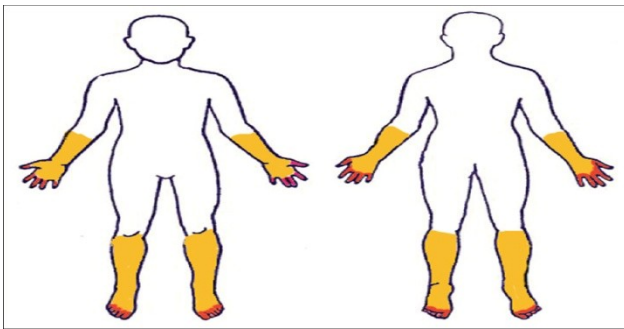
1. Enumerate symptoms & signs?

2. what is the probable diagnosis?

3. what are the function of thiamine (vitamin B1)?

4. Explain the biochemical basis of symptoms

enlargement. Lab revealed **decreased urinary thiamine level.**



Neurotropic vitamins



Vitamin B complex

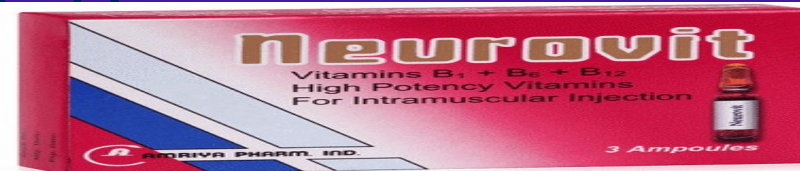
- Thiamine (B1)
- Riboflavin (B2)
- Nicotinic acid (B3)
- Pantothenic acid (B5)
- Pyridoxine (B6)
- Biotin
- Folic acid (B9)
- Cobalamins (B12)

“**Neurotropic**” B vitamins :
are especially important for the
healthy nervous system

“**neurotropic**”.

This group of **vitamins** is composed
of :

- Thiamine (B1)
- Niacin (B3)
- Pyridoxine (B6)
- Cyanocobalamin (B12) .
- Healthy CNS also need vitamin E



Food sources of vitamin B complex



All

1. Animal Sources:

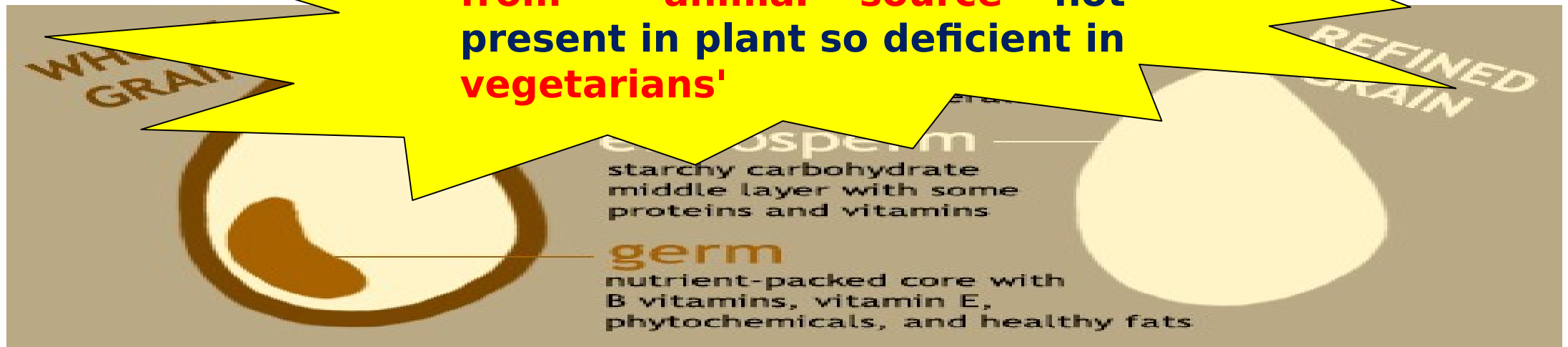
- Heart, liver, kidneys, meats, fishes, eggs and milk
- **Intestinal bacteria** form most members of the vitamin B complex

2. Plant Sources:

Green leafy vegetables, legumes, fruits, cereals and **yeast** are good plant sources.

البلدى بالرده والشوفان

Vitamin B12 supplied **only**
from animal source not
present in plant so deficient in
vegetarians'



Vitamin B I (Thiamine or Anti-Beri Beri)



Active form : thiamine pyrophosphate (TPP).

Functions of TPP: act as coenzymes for

1-Acts as coenzyme for **oxidative decarboxylation** of α -keto acids:

e.g.:

- **Pyruvate dehydrogenase complex**
(pyruvate to → acetyl-CoA)
- **α -Ketoglutarate dehydrogenase complex**
(α -ketoglutarate to → succinyl-CoA)

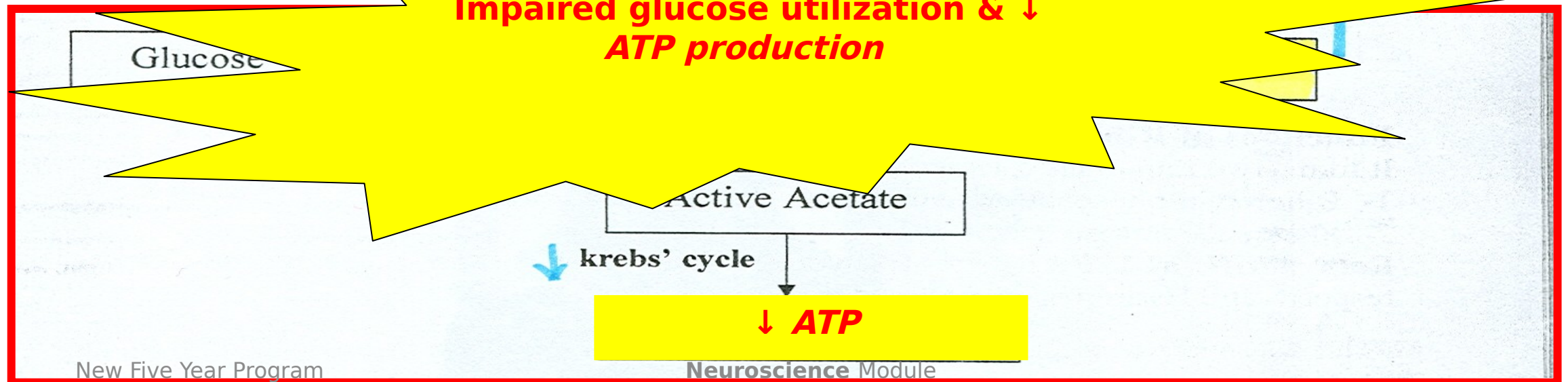
Vitamin B1 deficiency



Biochemical basis of clinical manifestations

- Pyruvate oxidation is impaired and pyruvate is converted to → lactate resulting in ↑ *blood* level of *pyruvate and lactate*.
- Also, Krebs cycle is affected due to ↓ activity of α-ketoglutarate (α-KG) dehydrogenase.

Impaired glucose utilization & ↓ *ATP production* will affect mainly nervous and muscular tissues, cardiac muscles.



Clinical manifestations (Beri-Beri)

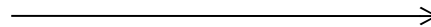


1-Early stage :Dry Beri Beri

- **Neurological Manifestation:**
Peripheral neuritis (Stock and gloves), mental confusion and muscular weakness.
- **GIT Manifestations:**
Anorexia, nausea and vomiting.

2-Late stage : Wet Beri Beri

- **Cardio-Vascular Manifestations:**
Cardiac enlargement, weakness and may be heart failure.
Edema (wet beri-beri).



Cardiovascular (wet) beriberi



"Pedal edema before and after the application of pressure to the shin."



Wernicke-Korsakoff syndrome

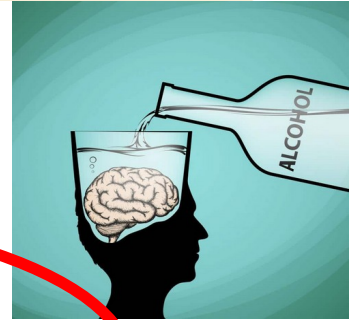


➤Causes

- Thiamine deficiency primarily in association with chronic alcoholism due to dietary insufficiency
- Or impaired intestinal absorption of the vitamin.

➤Characterized by:

- Confusion
- Ataxia,
- Rhythmic to-and-fro motion of the eyeballs (nystagmus)
- Memory problems
- Hallucinations



**Wernicke encephalopathy
(Acute reversible stage)**

**Korsakoff dementia
(chronic irreversible stage)**

chronic alcoholism

↓
thiamine deficiency

↓
brain tissue ischaemia
+ cell death

↓
WERNICKE'S

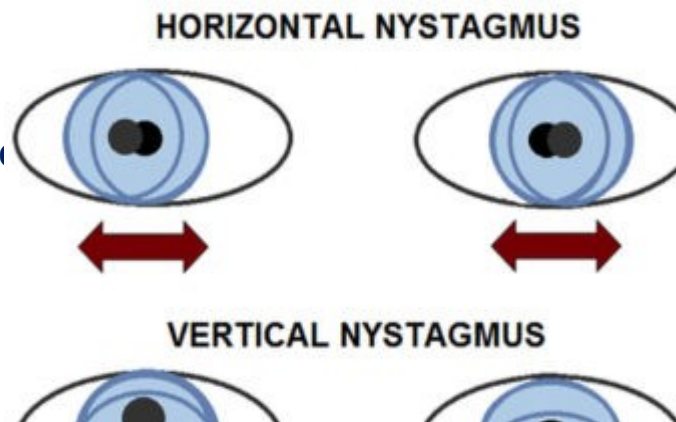
- 1. Acute confusional state
- 2. Ophthalmoplegia
- 3. ataxia

↓
KORSAKOFF'S

- 1. Amnesia
- 2. Confabulation
- 3. Psychosis

➤Treatment:

- Thiamine supplementation.
- Recovery of memory is incomplete

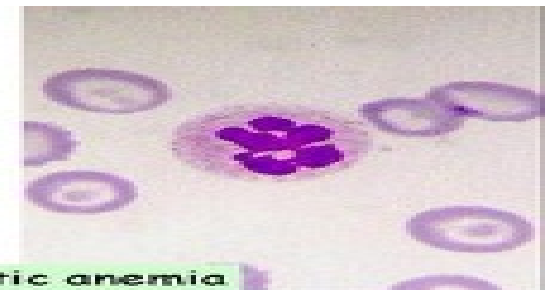
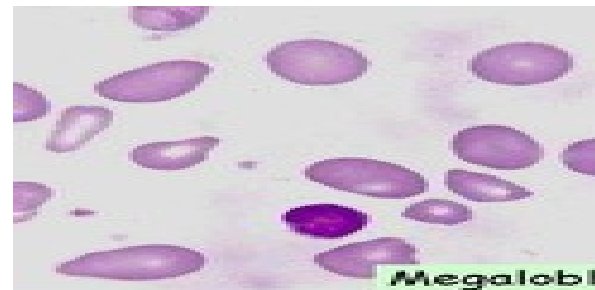
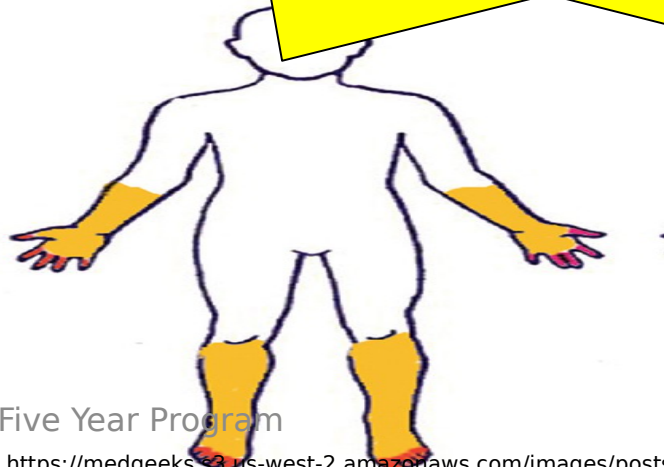


Cobalamin (Vitamin B 12) (Antipernicious Anemia)



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What is the suspected diagnosis?



Cobalamin (Vitamin B 12) (Antipernicious Anemia)

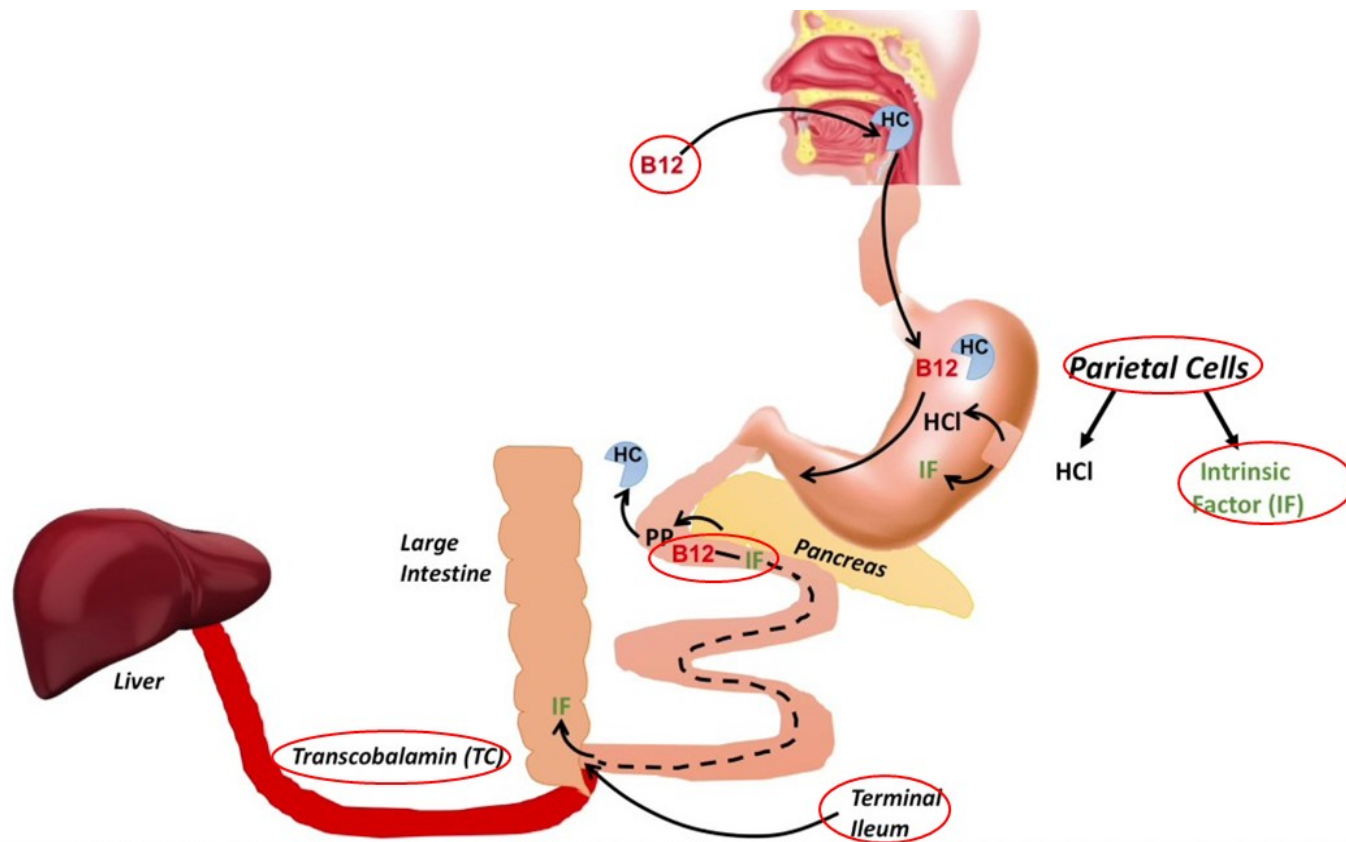


Source **Animal only** so deficient in vegetarians'.

Absorption:

- Vitamin B₁₂ (***extrinsic factor***) + IF (***intrinsic factor***) from parietal cells forming ***IF-B₁₂ complex***
- IF-B₁₂ complex in the gut binds to specific receptors on the mucosal cells of the **ileum**.
- B₁₂ is transported into the mucosal cells and then into **portal circulation**.
- Lack of IF prevents the absorption of vitamin B₁₂, resulting in **pernicious anemia**.

- cobalamin are transported in plasma as *Transcobalamin II-vitamin B12 complex*
- In the liver, cobalamin is **stored** attached to a protein (*transcobalamin I*). Liver stores provide up to **1-5 years** supply of B₁₂



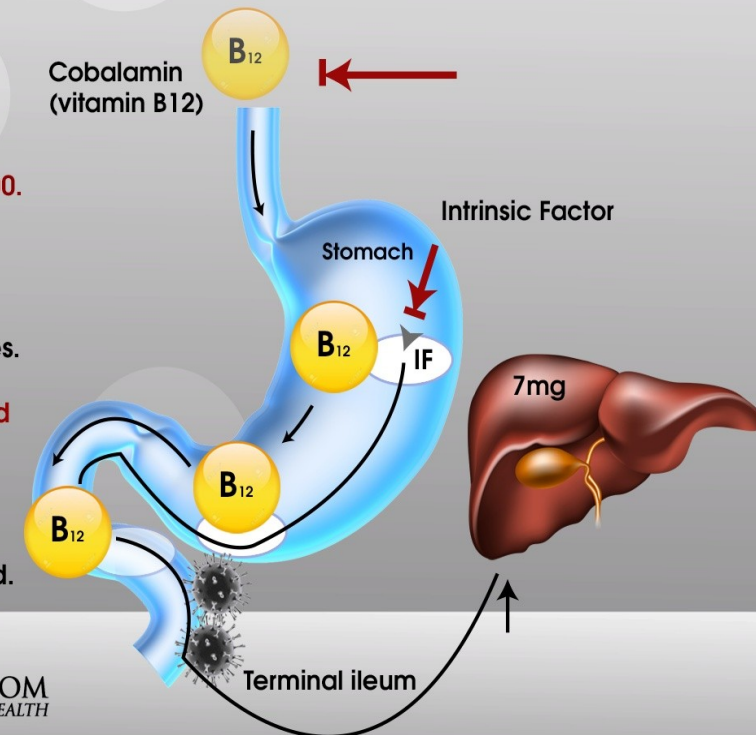
Absorption of Vitamin B12

Intrinsic factor is a glycoprotein of M.W. 4500.

Vit. B12 combine with intrinsic factor forming a complex that resist digestion by GIT enzymes.

This complex is absorbed at terminal ileum by pinocytosis.

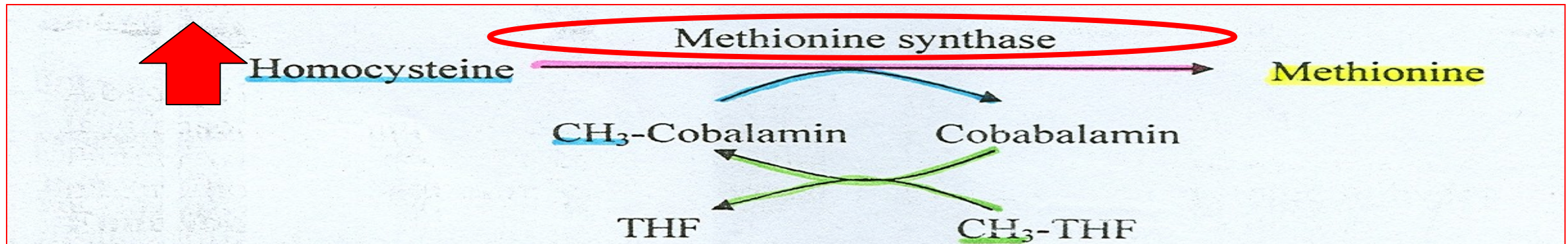
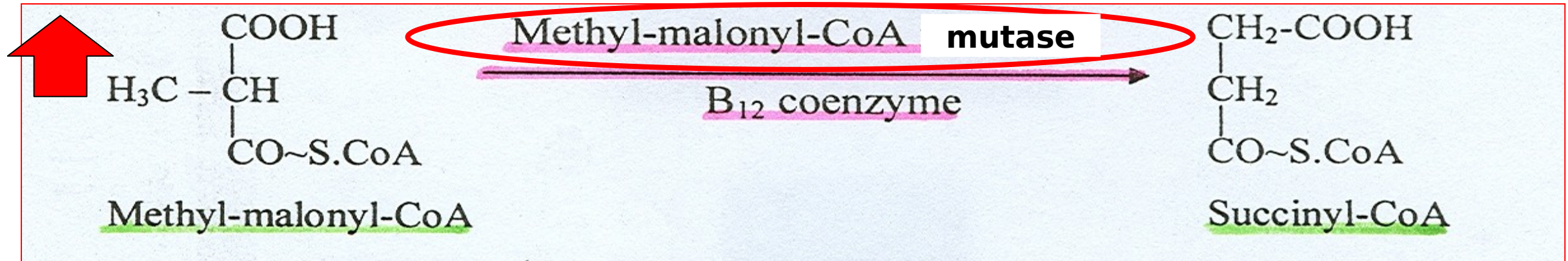
Vit. B12 is transported to the liver where it is stored.



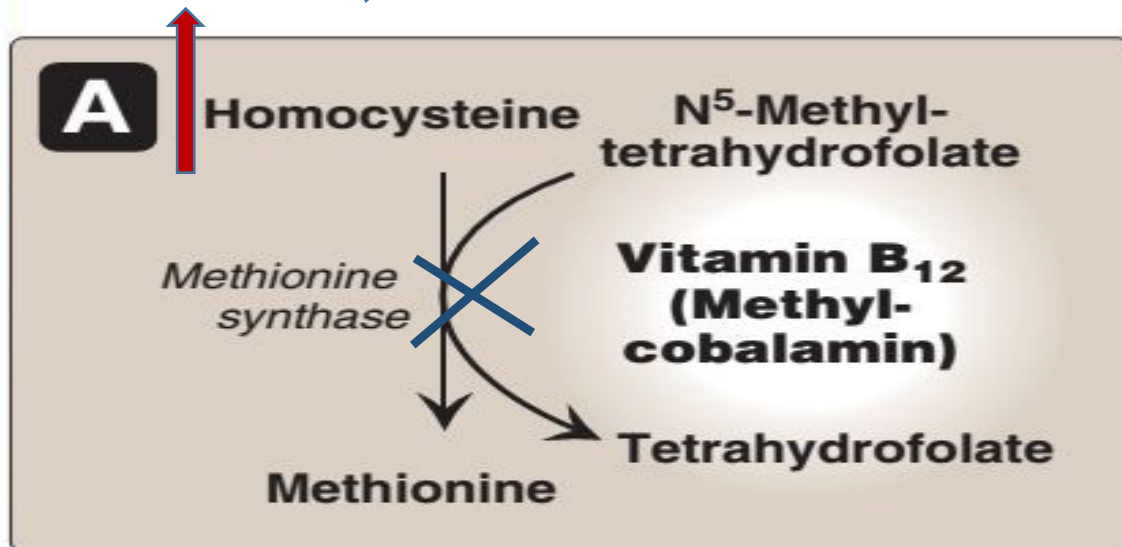
Function of Vitamin B12



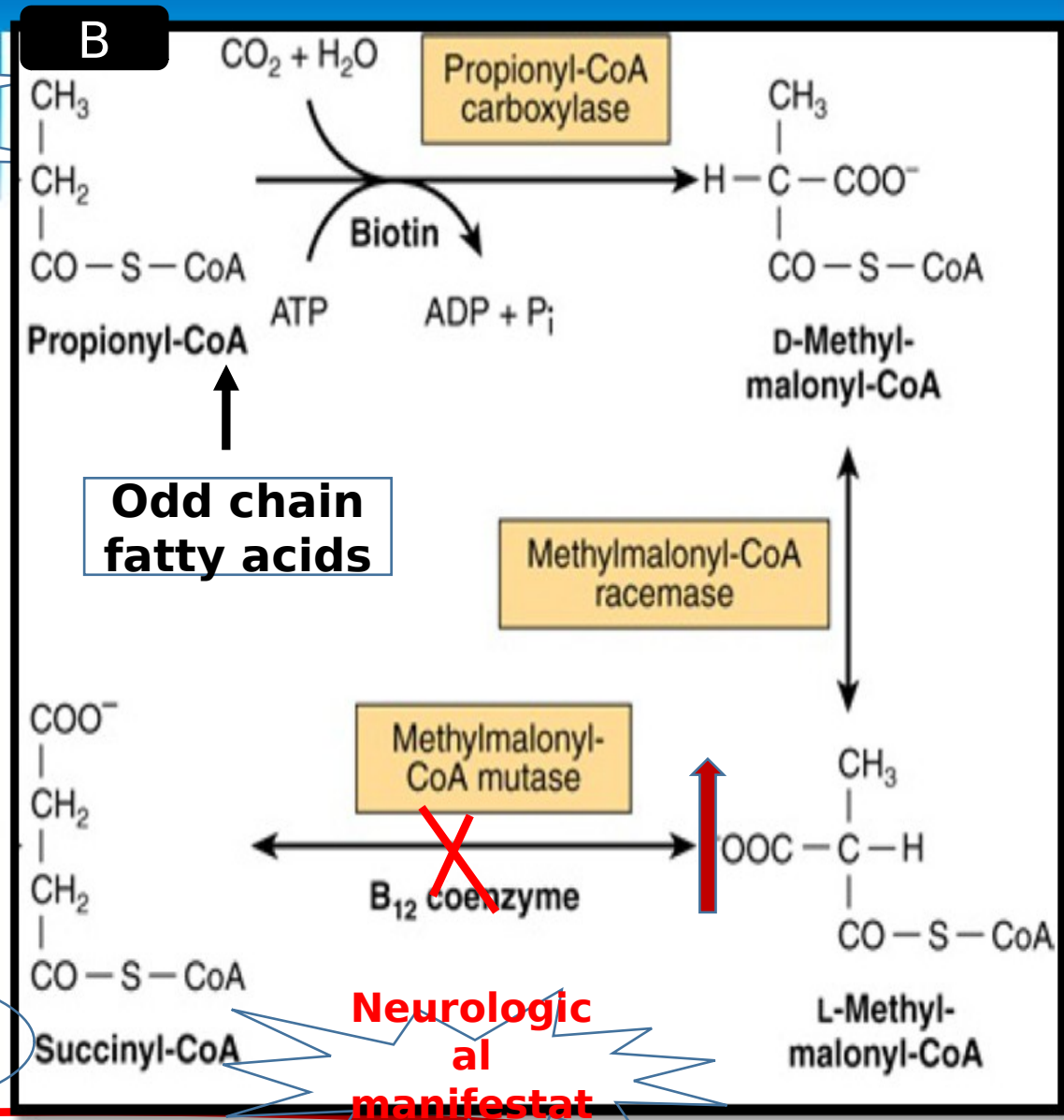
Acts as coenzyme for the following enzymes :



methylemalonyl CoA aciduria
found in urine in cases of vitamin
B12 deficiency



In vitamin
B12
deficiency



Reactions requiring coenzyme forms of vitamin B12.

Deficiency of Vitamin B12



Causes :

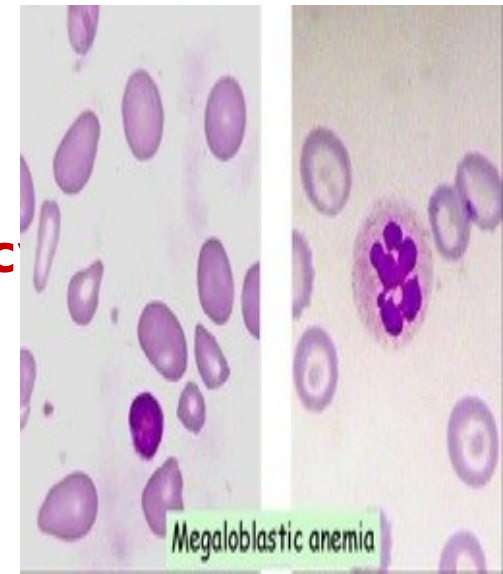
- **Failure of absorption of B₁₂**
 - Malabsorption diseases
 - Gastrectomy or operation for obesity treatment (Bypass operation & gastric sleeve; bariatric surgery) or gastric or small intestine resections
 - Autoimmune destruction of the gastric parietal cells (IF) → **pernicious anemia**
 - Malfunctioning of gastric parietal cells e.g. in **elderly subjects** → decreased secretion of intrinsic factor → B12 malabsorption.
 - Drugs as **antacids** as proton pump inhibitors which inhibit action of parietal cells cause decreased secretion of both B12 & HCL
- **Dietary deficiency** among **vegetarians**.

Manifestations :

A- Megaloblastic anemia or Leukopenia or thrombocytopenia or Pancytopenia due to **functional folate deficiency** which results in accumulation of **methyl-THF** leading to **folate trap**.

Neuroscience

Explain on a biochemical basis



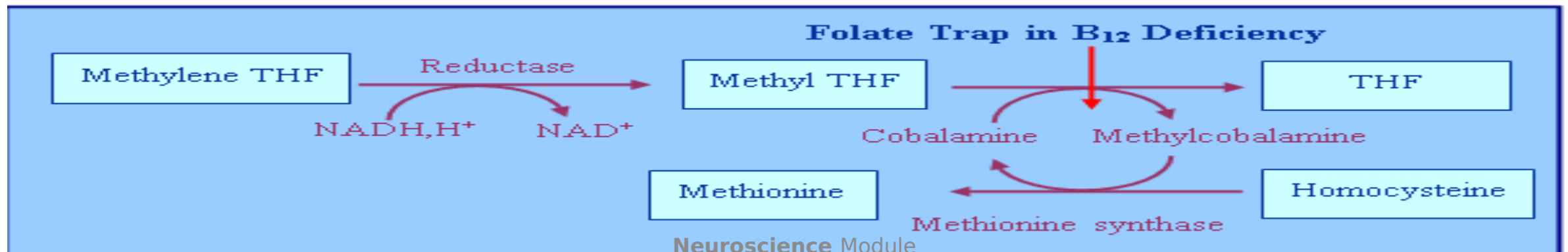
Folate trap (methyl folate trap)



The production of methyl THF is an irreversible step.
Therefore the only way to re-generate THF is mediated by cobalamine (**B₁₂**).

*In case of **cobalamine (B₁₂) deficiency** folate is trapped as methyl-THF.*

So it is a functional deficiency of folic acid



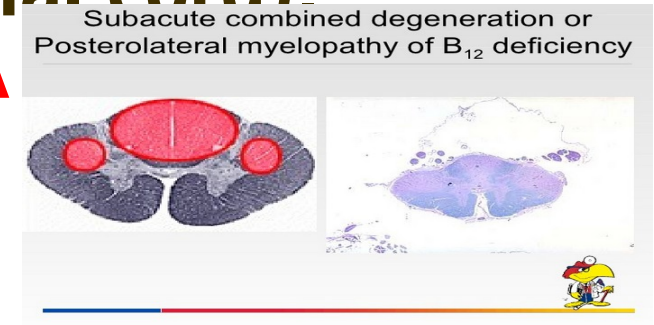
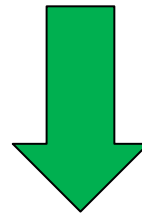
Deficiency of Vitamin B12



B- Neurological manifestations and methylmalonic aciduria :

- **Peripheral neuritis**
- **Sub acute combined degeneration of spinal cord (atrophy of the lateral and posterior columns of spinal cord)**

This is due to accumulation of methylmalonyl-CoA



1.acts as competitive for malonyl-CoA and produces inhibition of fatty acid biosynthesis required for synthesis of myelin sheath.

2- substitute malonyl-CoA in fatty acid synthesis leading to production of branched-chain fatty acids which disrupt membrane structure

Neurological manifestations of vitamin B12 deficiency



Neurological changes in B12 deficiency

1. Cerebrum:

- ✓ Complex neuropsychiatric symptoms: Delusion, illusion, hallucination, cognitive impairment, dementia, optic atrophy.

2. Spinal cord:

- ✓ Subacute combined degeneration of spinal cord
- ✓ Post column: Diminished vibration sensation and proprioception.
- ✓ Corticospinal tract: Upper motor neuron sign.

3. Peripheral Nerve:

- ✓ Tingling & numbness.
- ✓ Glove and stocking paraesthesia.
- ✓ Loss of ankle reflex.

- Peripheral nerves are usually affected first, and patients complain initially of paresthesias.
- The posterior columns next become impaired, and patients complain of difficulty with balance.

Deficiency of Vitamin B12



C-Hyperhomocysteinemia and thrombosis and hypertension:

- Elevated blood level of **homocysteine** is a significant risk factor for development of **atherosclerosis** and **hypertension** due to decrease of **methionine**:

- Methionine is **sulfur containing amino acid** enter in the
- Methionine is also needed for **S-Adenosyl methionine (SAM)** needed for **methylation reactions** during heparin synthesis.

Explain on a biochemical basis



- So the net result is defect in heparin structure & synthesis leads to defective functions of heparin thrombosis & hypertension

Manifest
e to fu

Increased homocysteine blood level of in :

- Vitamin B6 deficiency
- Vitamin B12 deficiency
- Folic acid deficiency

Neuroscience Module



Treatment of Vitamin B12 Deficiency



Vitamin B12 deficiency & anemia is usually treated with:

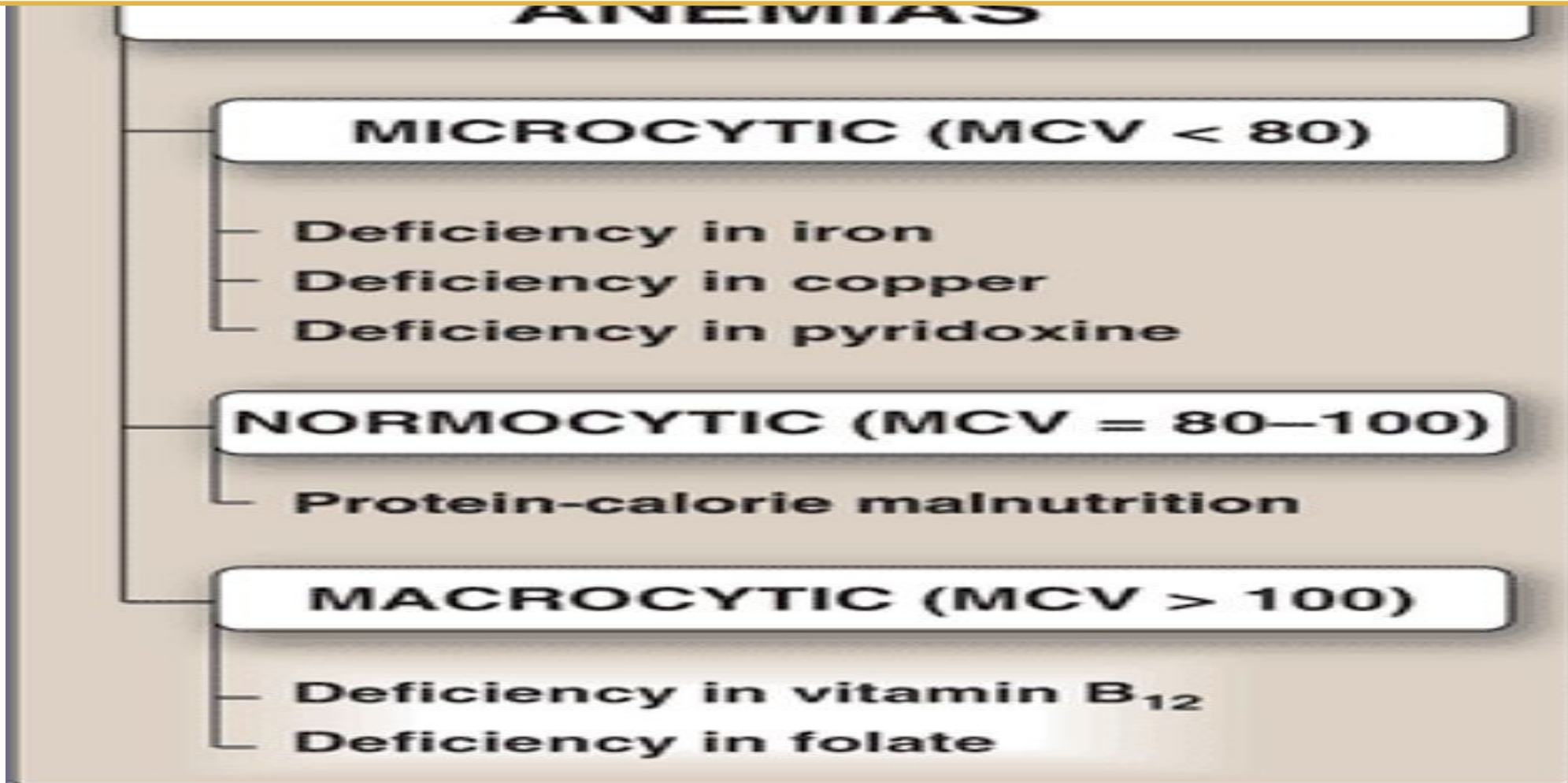
- **Intramuscular injections** of vitamin B12, in a form (**cyanocobalamin** or **hydroxocobalamin**). At first, these injections every other day for two weeks, or until symptoms have stopped and improving then every month for 2-3 months.
- Vitamin B12 not given orally & must given as **intramuscular injections** in the patient taking **antacids** drugs (**as** proton pump inhibitors or H2 blocker) because :
 - Antacids will decrease HCL secretion which is important for vitamin B12 absorption so it must be given as **intramuscular injections**
 - Some antacids inhibit action of part

Explain on a biochemical basis

 of both B12 & HCL decreasing B12 absorption
- Also if vitamin B12 deficient in diet as **vegetarian or vegan diet**: patient should take diet rich in vitamin B12 or vitamin B12 tablet in absence of antacids or other factor affecting its absorption as pernicious anemia & bariatric surgery or gastric or small intestine resections

Classification of nutritional anemia's by RBCs cell size

The normal mean corpuscular volume (MCV) for people older than age 18 is between 80 and 100 μm^3 .



USMLE Lecture Quiz



Which of the following is the coenzyme form of Thiamine?

- ☒ A) TPP (Thiamine pyrophosphate)
- ☐ B) TMP (Thiamine mono phosphate)
- ☐ C) TTP (Thiamine triphosphate)
- ☐ D) Free thiamine
- ☐ E) TAD (Thiamine adenine dinucleotide).

USMLE Lecture Quiz



A 42-year- old woman presents to physician with frontal headache , painful tongue & tingling & numbness over hand and feet. Examination revealed decreases sensation hand and feet ,hypertension & beefy red patch in the tongue. Laboratory investigation revealed megaloblastic anemia .

Which one of the following vitamin deficiency is suspected?

- A. Vitamin A**
- B. Vitamin B12**
- C. Vitamin B9**
- D. Vitamin B1**

SUGGESTED TEXTBOOKS



- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- Fundamentals of Clinical Chemistry (Tietz) Sixth
- "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- **www.namrata.co- *Biochemistry for medics***



Thank You

Dr. Amal El-Shal